PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P729PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2004/000205	International filing date *(day/month/year)* 25.03.2004	Priority date *(day/month/year)* 26.03.2003
International Patent Classification (IPC) or national classification and IPC A61K31/132, A61K31/16, A61K31/198, A61K31/4196, A61K31/445, A61K31/495, A61K31/53, A61K31/7008, A61P39/00, A61K31/00		
Applicant RECEPTICON APS et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.02.2005	04.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer A. Jakobs Telephone No. +31 70 340-2617

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000205

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-36	as originally filed
Claims, Numbers	
1-27	received on 15.02.2005 with letter of 15.02.2005
Drawings, Sheets	
1/7-7/7	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 28-61
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000205

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☒ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-11,17-19,25-26 (partially) 20-24,27

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-11,17-19,25-26 (partially) 20-24,27

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000205

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-19,25,26 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-10,12-14,16
	No:	Claims	1-4,11,15,17-19,25,26
Inventive step (IS)	Yes:	Claims	12-14,16
	No:	Claims	1-11,15,17-19,25,26
Industrial applicability (IA)	Yes:	Claims	See separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III.
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability.

Present claim 11 relates to a compound defined by reference to the following parameters: a medicament capable of binding to the receptor megalin or to the receptor cubilin. The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Present claims 1-11,17-19,25,26 relate to an extremely large number of possible compounds, i.e. 6 to over 20 membered rings containing two nitrogen atoms in positions 1,4. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. In response to the applicants letter dated 15 February 2005, it is maintained that the search has been carried out for those parts of the claims that appear to be supported and disclosed: For example, no single example covers claims 5-10, i.e. no diazathio-, diazadithio-, triaza-, tetraaza-, oxadiaza-, or dioxadiaza-heterocycles according to said formula VI are mentioned in the description.
Furthermore R4, R6 can not be independently selected from OH or Hydrogen because said compounds would not be compatible with the valencies commonly encountered in general organic chemical compounds (Cf. claim 1).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of individual compounds specified in claims 1 (partially),12-16 i.e. diaminomethane, 1,2-diaminoethane, 1,3-diaminopropane, 1,4.-diaminobutane, 1,5-diaminopentane or 1,6-diaminohexane, 1,7-diaminoheptane, 1,8-diaminooctane or the compounds of claims 12-15 in relation to the prophylaxis and/or treatment of induced cytotoxicity.

The ISR was drawn up in accordance with the PCT International Search and Preliminary

Examination Guidelines (2004) chapter 9, Section 9.19-9.25. When a meaningful search can be performed for only part of the subject-matter of a claim, this is no longer mentioned on the ISR but in the written opinion of the ISA.

No Written Opinion will be formulated with respect to subject matter which is not covered by the search report.

Re Item IV.

The separate inventions/groups of inventions presently on file are:

1. Claims 1-19,25,26 (partially)
   Use of a compound of formulae VI, or diaminomethane, 1,2-diaminoethane, 1,3-diaminopropane, 1,4.-diaminobutane, 1,5-diaminopentane or 1,6-diaminohexane, 1,7-diaminoheptane, 1,8-diaminooctane or the compounds of claims 12-15 for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity.
2. Claims 20-24,27
   A compound of formula VII and uses thereof.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem to be solved by the present application is to provide for the reduction, prophylaxis and/or treatment of induced cell toxicity.

The proposed solutions are to use a compound of formulae I-VI, use of a moiety of gentamicin (including garoseamine, purpuroseamine or 2-deoxystreptamine), to provide for compounds of general formula (VII), and to reduce the number of cationic groups from at least one cell toxic compound by e.g. introducing an amide group into said compound.

WO03080103 discloses polylysine and other polyamino compounds which are compounds according to claim 1 and inhibitors of megalin and cubulin which reduce gentamycin nephrotoxicity and ototoxicity. See the passages cited in the search report.

WO02053519 discloses polyamine analogs or derivatives according to claim 1 which are useful to treat cancer, said compounds are also useful to reduce hearing loss resulting from chemotherapy. Furthermore, compounds according to claim 42 of formula (VII) are disclosed herein. See the passages cited in the search report.

WO9902145 discloses the treatment of infections in a mammal comprises administering (a) an aminoglycoside antibiotic (e.g gentamicin, ...) and (b) a N,N' or N,N-disubstituted, N,N,N'-trisubstituted, N,N,N' or N'-tetrasubstituted-guanidine optionally containing 5,6 or seven membered nitogen containing rings and ring systems: the combined use decreases the ototoxicity of the aminoglycoside antibiotic alone.

DE10053506 discloses composition for preventing kidney, and inner ear organ damage caused by aminoglycosides and derivatives (A) contains a megalin receptor antagonist (I) (e.g. polymyxin, a cyclic poly amino compound which inhibits the binding of aminoglycosides (A) to megalin or displaces aminoglycosides (A) from megalin receptors. See the passages cited in the search report.

GB1364521 discloses acetylated gentamicin derivatives with a reduced number of cationic groups with increased toxicity for resistant strains of gram positive and gram-negative microorganisms which posses advantages over the parent gentamicin derivatives according to the method of present claim 50-57. See the passages cited in the search report.

According to Article 3(4)(iii) PCT, an international application shall comply with "the prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

From the above cited documents, it appears that the use the compounds of the present invention in relation to reducing the cytotoxicity induced by chemotherapy is known in the prior art and can not fulfil the role of special technical feature (general inventive concept) in the sense of Rule 13.2 PCT.

Accordingly there is no new technical effect linking the different groups of inventions.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Consequently the present application lacks unity of invention.

As searching the other inventions would have caused a major additional searching effort, only the first invention was searched.

No Report will be established with respect to subject matter which is not covered by the search report.

Re Item V.
Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The attention of the Applicant is drawn to the fact that present opinion regarding novelty, inventive step and industrial applicability is only established with regard to subject matter for which an international search report has been established i.e. the use of individual compounds specified in claims 1 (partially),12-16 i.e. diaminomethane, 1,2-diaminoethane, 1,3-diaminopropane, 1,4.-diaminobutane, 1,5-diaminopentane or 1,6-diaminohexane, 1,7-diaminoheptane, 1,8-diaminooctane or the compounds of claims 12-15 in relation to the prophylaxis and/or treatment of induced cytotoxicity.

1 The following document is referred to in this communication:

D1 : GB 1 364 521 A (MERCK & CO INC) 21 August 1974 (1974-08-21)
D2 : WO 02/053519 A (BURNS MARK ROBERT ; BANDUIR NAND (US); ORIDIGM CORP (US); GRAMINSKI GE) 11 July 2002 (2002-07-11)
D3 : WO 99/02145 A (DURANT GRAHAM J ; GWYNNE DAVID I (US); CAMBRIDGE NEUROSCIENCE INC (US)) 21 January 1999 (1999-01-21)
D4 : EP 0 483 634 A (HOECHST ROUSSEL PHARMA) 6 May 1992 (1992-05-06)
D5 : DE 100 53 506 A (MAX DELBRUECK CENTRUM) 2 May 2002 (2002-05-02)

D6 : WO 89/05637 A (US BIOSCIENCE) 29 June 1989 (1989-06-29)
D7 : US 6 177 434 B1 (KOPKE RICHARD D ET AL) 23 January 2001 (2001-01-23)
D8 : US 6 130 217 A (ARNOLD LEE DANIEL ET AL) 10 October 2000 (2000-10-10)
D9 : MILAM K M ET AL: "REDUCTION IN CIS DIAMMINEDICHLOROPLATINUM-II-INDUCED CYTOTOXICITY SISTER CHROMATID EXCHANGE AND DNA INTERSTRAND CROSS-LINKS IN 9L CELLS TREATED WITH THE POLYAMINE BIOSYNTHESIS INHIBITOR 2R 5R-6 HEPTYNE-2 5-DIAMINE" CANCER RESEARCH, vol. 49, no. 24 PART 1, 1989, pages 6945-6948, XP008033957 ISSN: 0008-5472
D10 : HEYS, STEVEN D. ET AL: "Potentiation of the response to chemotherapy in patients with breast cancer by dietary supplementation with L-arginine: results of a randomized controlled trial" INTERNATIONAL JOURNAL OF ONCOLOGY , 12(1), 221-225 CODEN: IJONES; ISSN: 1019-6439, 1998, XP008033963
D11 : TOMIDA A ET AL: "NOVEL MECHANISM OF N SOLANESYL-N N'-BIS-3 4-DIMETHOXYBENZYLETHYLENEDI AMINE IN POTENTIATION OF ANTITUMOR DRUG ACTION ON MULTIDRUG-RESISTANCE AND SENSITIVE CHINESE HAMSTER CELLS" JAPANESE JOURNAL OF CANCER RESEARCH, vol. 82, no. 1, 1991, pages 127-133, XP008033945 ISSN: 0910-5050
D12 : WO 01/12607 A (DARRO FRANCIS ; KISS ROBERT (BE); GUILLAUMET GERALD (FR); JOSEPH BENOI) 22 February 2001 (2001-02-22)
D13 : FAN DOMINIC ET AL: "Reversal of multidrug resistance in murine fibrosarcoma cells by thioxanthene flupentixol" INVESTIGATIONAL NEW DRUGS, vol. 12, no. 3, 1994, pages 185-195, XP008033946
D14 : WIEBKIN P ET AL: "INHIBITION OF METABOLISM MEDIATED CYTO TOXICITY BY 1 1 DI SUBSTITUTED HYDRAZINES IN MOUSE MASTO CYTOMA LINE P-815 CELLS" BIOCHEMICAL PHARMACOLOGY, vol. 31, no. 18, 1982, pages 2921-2928, XP001199476 ISSN: 0006-2952
D15 : KONDRATOV R V ET AL: "Small molecules that dramatically alter multidrug resistance phenotype by modulating the substrate specificity of P-glycoprotein" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 98, no. 24, 20 November 2001 (2001-11-20), pages 14078-14083, XP002259950 ISSN: 0027-8424

2 Novelty: CLAIMS 1-4,11,15,17-19,25,26

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D2 discloses (See the passages cited in the search report) polyamine analogs or derivatives according to said claims which are useful to treat cancer, said compounds are also useful to reduce hearing loss resulting from chemotherapy and are most preferably administered in combination with e.g 1,3-diaminopropane (cf. page 36).

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D3 discloses (See the passages cited in the search report) the treatment of infections in a mammal comprises administering (a) an aminoglycoside antibiotic (e.g gentamicin, ...) and (b) a N,N' or N,N-disubstituted, N,N,N'-trisubstituted, N,N,N' or N'-tetrasubstituted-guanidine optionally containing 5,6 or seven membered nitrogen containing rings and ring systems according to formula VI (see for example p. 90 line 11-12): the combined use decreases the ototoxicity of the aminoglycoside antibiotic alone.

2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D5 discloses (See the passages cited in the search report) composition for preventing kidney, and inner ear organ damage caused by aminoglycosides and derivatives (A) containing a megalin receptor antagonist (I) (e.g. polybasic compounds i.e. polymyxin, a cyclic poly amino compound of the formulae of claims 1-4,11,17-19,25,26) which inhibits the binding of aminoglycosides (A) to megalin or displaces aminoglycosides (A) from megalin receptors together with said aminoglycosides. Said compounds are compounds according to formula VI comprising a.o. R1 and R2 groups optionally substituted by the substituents of claim 1 which may be substituted one or more times with the substituents listed in claim 1 thereby providing for the possibility of a long "tail" of polymyxin.

2.4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D8 discloses (see the passages cited in the search report) amino

cpds. of formula NRoR1R2 which are diamino or polyamino compounds according to said claims, including piperazine compounds, useful for sensitising tumour cells to anticancer agents and as sensitisers of multidrug resistant forms of malaria (Plasmodium falciparum), tuberculosis, leishmania and amoebic dysentery. They increase the activity/efficacy of e.g. adriamycin, daunomycins, etoposide, topotecan, teniposide, actinomycin D, taxol, vincristine, vinblastine and anthracycline antibiotics.

2.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,15,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D9 discloses (see the passages cited in the search report) the use of the polyamine biosynthesis inhibitor 2R,5R-6-heptyne 2,5-diamine to reduce cis-platin induced cytotoxicity and discloses that the addition of the diamine putresceine (1,5-diaminopentane) increases the effect.

2.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D12 discloses (see the passages cited in the search report) pharmaceutical compositions that act on the proliferation of clonogenic cells in tumors and contain 4-quinolone derivatives which fall under the structural definitions of present claims (see example 61). They are not cytotoxic agents, but they increase the effectiveness of known cytotoxic agents and consequently allow to reduce the severity of side effects by lowering the dosage of the cytotoxic agents.

2.7 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-4,11,17-19,25,26 is not new in the sense of Article 33(2) PCT. Document D13 discloses (see the passages cited in the search report) the reversal of multidrug resistance in murine fibrosarcoma cells by thioxanthene flupentixol, a piperazine substituted thioxanthene compound according to said claims. Thioxanthene flupentixol is not a cytotoxic agent but it increases the effectiveness of known cytotoxic agents and consequently allow to reduce the severity of side effects by lowering the dosage of the cytotoxic agents.

3. Inventive step: CLAIMS 1-11,15,17-19,25,26

3.1 The subject matter of claims 1-11,15,17-19,25,26 (as far as novel), does not involve an inventive step in the sense of Art, 33(3) PCT because no single example covers claims 5-10, i.e. no diazathio-, diazadithio-, triaza-, tetraaza-, oxadiaza-, or dioxadiaza-heterocycles according to said formula VI are mentioned in the description.

3.2 The subject matter of claims 1-11,15,17-19,25,26 (as far as novel), does not involve an inventive step in the sense of Art, 33(3) PCT because Document D9 discloses (see the passages cited in the search report) the use of the polyamine biosynthesis inhibitor 2R,5R-6-heptyne 2,5-diamine to reduce cis-platin induced cytotoxicity and discloses that the addition of the diamine putresceine (1,5-diaminopentane) increases the effect. Since D9 discloses that 1,5-diaminopentane has an effect opposite to the presently claimed effect, it is not credible that the existing technical problem is solved throughout the whole scope of said claims.

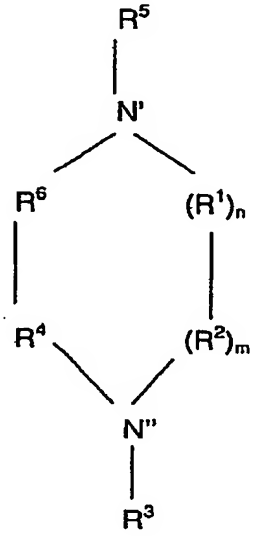
3.3. The same reasoning applies to claims 5-10, i.e. no diazathio-, diazadithio-, triaza-, tetraaza-, oxadiaza-, or dioxadiaza-heterocycles according to said formula VI, let alone e.g. compounds with 2-16 Oxygen-oxygen bonds are provided for in the description. It is therefore not credible that the technical problem is solved over the whole scope of the claim said compounds failing a.o. to satisfy the criteria of being produced in a credible way.

10/550488

JC05 Rec'd PCT/PTO 26 SEP 2005

Claims

1. Use of a compound comprising a structure of the general formula (VI)



(VI)

wherein

each R^1 and each R^2 independently are selected from C, S, N, O, optionally substituted with C, S, N, O, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C_{1-4})-alkyl, heteroaryl-(C_{1-4})-alkyl, heterocyclyl-(C_{1-4})-alkyl, cycloalkylalkyl, cycloalkyl, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C_{1-4})-alkyl, heteroaryl-(C_{1-4})-alkyl, heterocyclyl-(C_{1-4})-alkyl, cycloalkylalkyl, cycloalkyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and wherein

$_m$ is an integer of from 1 to 8,

$_n$ is an integer of from 1 to 8,

N' and N" are nitrogen,

R^3, R^4, R^5 and R^6 are independently selected from C, S, N, O, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C_{1-4})-alkyl, heteroaryl-(C_{1-4})-alkyl, heterocyclyl-(C_{1-4})-alkyl, cycloalkylalkyl, cycloalkyl, optionally further substituted one or more

times with C, S, N, O, OH, phenyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C_{1-4})-alkyl, heteroaryl-(C_{1-4})-alkyl, heterocyclyl-(C_{1-4})-alkyl, cycloalkylalkyl, cycloalkyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro,

or one or more of R^3, R^4, R^5 and R^6 is a chemical bond,

or a pharmaceutically acceptable addition salt or hydrate thereof,

or diaminomethane, 1,2-diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, 1,5-diaminopentane, 1,6-diaminohexane, 1,7-diaminoheptane, 1,8-diaminooctane,

or a pharmaceutically acceptable addition salt or hydrate thereof,

for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity

2. The use according to any of the preceding claims, wherein said cell presents the receptor megalin and/or the receptor cubilin.

3. The use according to any of the preceding claims, wherein at least one of R^1 or R^2 is C.

4. The use according to claim 1 or 2, wherein R^1 and R^2 are C.

5. The use according to claim 1 or 2, wherein at least one of R^1 or R^2 is S.

6. The use according to claim 1 or 2, wherein R^1 and R^2 are S.

7. The use according to claim 1 or 2, wherein at least one of R^1 and R^2 is N.

8. The use according to claim 1 or 2, wherein R^1 and R^2 are N.

9. The use according to claim 1 or 2, wherein at least one of R^1 and R^2 is O.

10. The use according to claim 1 or 2, wherein R^1 and R^2 are O.

11. The use according to any of the preceding claims, wherein the medicament is capable of binding to the receptor megalin and/or the receptor cubilin.

12. The use according to claim 1, wherein the compound is selected from 3-methylamino-1-(4-methylpiperazino)-2-propanole, 4-piperazinoaniline, 1-(3-chlorophenyl)piperazine diHCl (m-CPP), piperazin-2-one-HCl, 2-[4-(2-aminoethyl)-piperazin-1-yl] ethylamine, piperazine anhydrous, 2,4-diamino-6-phenyl-1,3,5-triazine, 3,5-diamino-1,2,4-triazole, 2,5-piperazinedione, piperazine, piperazin-2-one-HCl, 1-(2-pyrimidyl)piperazine dihydrochloride, or a pharmaceutically acceptable addition salt or hydrate thereof.

13. The use according to claim 12, wherein the compound is selected from 2-[4-(2-aminoethyl)piperazin-1-yl] ethylamine, 3-methylamino-1-(4-methylpiperazino)-2-propanole, and piperazine.

14. The use according to claim 1, wherein the compound is piperazine.

15. The use according to claim 1, wherein the compound is selected from 1,7-diaminoheptane, 1,2-diaminoethane, 1,4-diaminobutane, 1,6-diaminohexane, and 1,5-diaminopentane.

16. The use according to claim 1, wherein the compound is 1,6-diaminohexane.

17. The use according to any of the preceding claims, wherein the cell is from the kidney and/or the inner ear.

18. The use according to any of the preceding claims, wherein said compound in solution has at least 1, such as at least 2 positive charges, for example at least 20 positive charges.

19. The use according to any of the preceding claims, wherein said compound has a polybasic charge distribution.

20. A compound having the general formula of

$(A_q - X)_p$ (VII)

wherein
A is a compound as defined in any one of claims 1-19, and wherein
X is a spacer,
q is an integer of 1-100,
p is an integer of 1-100.

21. The compound according to claim 20, wherein the spacer is a covalent bond.

22. The compound according to claim 20, wherein the spacer consists of from 2-12 atoms, such as C-atoms, for example from 4-10 atoms, such as C-atoms, preferably from 6-8 atoms, such as C-atoms.

23. Use of a compound as defined in claim 20, for the prophylaxis and/or treatment of induced cell toxicity.

24. Use of a compound as defined in claim 20, wherein the use is defined in any one of claims 1-19.

25. A combination medicament comprising a compound as defined in any of the claims 1-19 and a therapeutic agent for simultaneous, separate or sequential use in induced cell toxicity therapy.

26. The combination medicament according to claim 25, wherein said cell presents the receptor megalin and/or the receptor cubilin.

27. A pharmaceutical composition comprising a compound as defined in any of claims 20-22 and pharmaceutically acceptable carriers, excipients or diluents therefor.